**REMARKS**

Claims 1-34 were pending in the subject application. Applicants have by this Amendment amended claims 1, 2, 5, 12, 13, 32 and 33, and added new claims 35 and 36. Accordingly, claims 1-36 are presented for the Examiner's reconsideration.

Claim 1 has been amended, *inter alia*, to incorporate the limitations of claim 2. Thus, support for the amended claim 1 appears throughout the specification as it does for claim 2.

**Request to examine withdrawn claims**

In Section 1 of the January 6, 2003 Office Action, the Examiner indicated that the August 29, 2002 restriction requirement is being maintained until a linking claim is found allowable. In view of applicants' amendments to claim 1 as explained in more detail below, applicants contend that amended claim 1 is allowable over the art cited. As explained in applicants' September 30, 2002 Response to the August 29, 2002 restriction requirement, claim 1 is a linking claim to both of the formulas IA and IB, and to the method claims 25-31. Accordingly, examination of all of the pending claims is respectfully requested pursuant to M.P.E.P. §§ 806.05(i) and 809, *et seq.*

**Rejection under 35 U.S.C. § 112, second paragraph**

In Section 6 and 7 of the January 6, 2003 Office Action, the Examiner rejected claims 7-10, 24, and 32-34 under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner alleged that claim 7 does not have antecedent basis for the recitation of the class "WYHH".

In response, applicants point out that WYHH falls within the class DYHH of claim 5. However, to expedite prosecution, applicants have amended claim 5 to provide an antecedent basis for the recitation of WYHH in claim 7.

With respect to claims 32-34, the Examiner alleged that the phrase "capable of hybridizing with," is vague and indefinite since applicants have not allegedly defined the conditions of hybridization wherein the compounds of the present invention are capable of hybridizing to a target sequence.

In response, without conceding the correctness of the Examiner's position, but merely to advance prosecution, applicants have amended claims 32-34, and the similar phrase in claim 1, to recite "hybridizes."

No reason is provided by the Examiner for inclusion of claim 24 in this rejection, and such is presumed to be an error.

Accordingly, applicants respectfully submit that the rejection under 37 C.F.R. § 112, second paragraph, should be reconsidered and withdrawn.

**Rejection under 35 U.S.C. § 102 - Wang et al.**

The Examiner rejected claims 1, 2, 4-5, and 32 under 35 U.S.C. §102(b) as allegedly anticipated by Wang et al. (Biochemical and Biophysical Research Communication (1998), 250(3), 711-719). The Examiner alleged that Wang et al. disclose the hammerhead ribozyme sequence according to 5'-AAA-CUU-CGA-GAC-GAC-UGA-UGA-GGC-GCU-CGA-AAG-3' [sic] (referring to page 714, Hrbz, X2=A and X1=G). The Examiner then alleged that this sequence corresponds to the sequence wherein: (X)n' is AAA-CUU-CGA-GAC-GA, 'X' is "U", (X)a is G, NNHH is CGCU, and (X)n is AG, and that the ribozyme

structure of Wang et al. meets the structural limitations of the formula according to structure 1A of claim 1. The Examiner additionally alleged that the 3'-(X)n1 nucleotide of Wang et al. is "A", and n+n' is greater than 14.

Th Examiner also alleged that Wang et al. disclose the following compound: 5'-A-A-A-C-U U-C-G-A-G-A-C-G-A-C-U-G-A-U-G-A-G-G-C (oxyphosphinicooxy-1, 3-propanediylosyphosphinicooxy)C-U-C-G-A-A-G-G-3' (again referring to page 714, Hrbz, X2=A and X1=non-nucleotide linker), and that this sequence is encompassed by the compound according to structure 1A wherein (X)a is absent, and furthermore wherein the linker sequence 5'-NNHH-3' and 5'DYHH-3' has a sequence according to 5'-GCCU-3'. The Examiner noted that the (X)n regions function in an antisense manner and therefore these regions can be considered antisense oligonucleotide structures. The Examiner then concluded by asserting that Wang et al. teach each and every aspect of the instant invention thereby anticipating applicant's claimed invention.

In response, applicants initially point out that the Examiner incorrectly cited the penultimate nucleotide of the Hrbz sequence of Wang et al. in the first of the two times the Examiner has referred to the Hrbz sequence. Specifically, in the first reference, the Examiner incorrectly cited the purported 3' end of the Hrbz sequence as ...CGA-AAG-3', whereas it is actually ...CGA-A**G**G-3'. The Examiner's second reference to the Hrbz sequence included the correct citation of the sequence, ...CGA-A**G**G-3'.

When correctly cited, Hrbz of Wang et al. does not anticipate applicants' amended claim 1. Applicants have by this Amendment incorporated the limitation of claim 2 into structure IA of claim 1. As amended, claim 1, structure IA, requires that the compound

contain the sequence ...CGAAA-$(X)_{n-1}$-3', which is not anticipated by Wang et al.

Accordingly, the rejection under 35 U.S.C. § 102 based on Wang et al. should be reconsidered and withdrawn.

**Rejection under 35 U.S.C. § 102 - Akhtar et al.**

In Section 10 of the January 6, 2003 Office Action, the Examiner rejected claims 1-2, and 15-24 under 35 U.S.C. §102(b) as allegedly anticipated by Akhtar et al. (WO 98/33893). The Examiner alleged that Akhtar et al. disclose a ribozyme comprising the following sequence: 5'-G-U-C-C-U-G-G-G-C-U-G-A-U-G-A-N-G-A-A-A-U-C-G-A-A-A-G-3' (referring to Table III, SEQ ID NO: 1274). The Examiner alleged that this ribozyme comprises a sequence encompassed by structure 1A as recited in claim 1 of the instant application wherein (X)n' is G-U-C-C-U-G-G-G, X' is U, (X)a is N, NNHH is AAAU, and (X)n is AG.

The Examiner also alleged that Akhtar et al. disclose ribozymes complexed with cationic lipids, packaged within liposomes for delivery to target cells (page 9, lines 31-34); and that the ribozymes may also be expressed from transcription units inserted into DNA or RNA vectors, preferably DNA plasmids or viral vectors (see page 11, lines 11-30); and that the ribozyme encoding sequences incorporated into a DNA or RNA expression vector may be driven by promoter sequences from RNA polymerase I, II or polymerase III, in addition prokaryotic RNA polymerase promoters may also be used; and that these ribozyme transcription units may be expressed in prokaryotic cells and mammalian cells. (see all of page 22).

In response, applicants respectfully traverse the Examiner's rejection on the ground that the sequence in Akhtar et al. does not anticipate applicants' claims. Specifically, the Examiner cited the SEQ. ID 1274 of Akhtar et al. as "5'-G-U-C-C-U-G-G-G-C-U-G-A-U-G-A-***N***-G-A-A-A-U-C-G-A-A-A-G-3'" (emphasis added), whereas Akhtar et al. actually disclose "5'-G-U-C-C-U-G-G-G-C-U-G-A-U-G-A-***X***-G-A-A-A-U-C-G-A-A-A-G-3'", and in the footnote to Table III on page 85 specifies that the ***X*** "represents stem II region of a HH ribozyme (Hertel et al., 1992 Nucleic Acid Res. 20 3252). The length of stem II may be ≥2 base-pairs." Thus, ***X*** in the Akhtar et al. sequence does not merely represent a single nucleotide as the Examiner alleged. The Examiner's rejection, as stated, is thus moot.

Applicants note that the precise meaning of the footnote to Table III of Akhtar et al. is unclear. For the purpose of this discussion only, assuming the footnote means that ***X*** may be any stem II region of a hammerhead (HH) ribozyme, and the reference to Hertel et al. is merely a reference to clarify the hammerhead nomenclature, then Akhtar et al. discloses a hammerhead ribozyme with a generic stem II region which does not anticipate applicants' claimed ribozymes active at low magnesium concentrations. Such an interpretation appears supported by page 19, lines 8-17, of Akhtar et al., and by the fact that Hertel et al. is only concerned with nomenclature of hammerhead ribozymes. However, if for the purposes of this discussion only, we assume the footnote means that ***X*** is the stem II region of any one of the two (2) hammerhead ribozymes exemplified in Hertel et al., then neither of the exemplified stem II regions when inserted in place of ***X*** in Akhtar et al. results in a sequence that anticipates applicants' claims. Applicants offer these possible

interpretations solely for the purposes of alerting the Examiner to the lack of clarity in the footnote. Therefore, applicants respectfully request that the Examiner independently review this footnote and the relevance of Akhtar et al. to applicants' claims.

To assist the Examiner in further evaluating the Akhtar et al. disclosure, applicants attach with the accompanying Information Disclosure Statement as **Exhibit B** a copy of Hertel et al. 1992 Nucleic Acid Res. 20 3252.

**Rejection under 35 U.S.C. § 102 - Zwick et al.**

In Section 11 of the January 6, 2003 Office Action, the Examiner rejected claims 1-2 under 35 U.S.C. § 102(b) as allegedly anticipated by Zwick et al. (WO 98/32843). The Examiner alleged that Zwick et al. disclose a ribozyme having the following formula: 5'-GGCUGAUGCUGAUGANGAAAACGAAAA-3' (referring to Table V, page 52, ribozyme targeting position #10). The Examiner alleged that this ribozyme comprises a sequence encompassed by structure 1A as recited in claim 1 of the instant application, specifically wherein the 5'-NNHH-3' sequence is 5'-AAAA-3'.

In response, Zwick et al. like Akhtar et al. disclose an ***X*** in its sequence on page 52, targeted to position 10, not an **N** as the Examiner alleged. Like in Akhtar et al., the ***X*** in Zwick et al. is defined in the footnote to Table V on page 59 to represent "stem II region of a HH ribozyme (Hertel et al., 1992 Nucleic Acid Res. 20 3252). The length of stem II may be ≥2 base-pairs." Thus, ***X*** in the Zwick et al. sequence does not merely represent a single nucleotide as the Examiner alleged. The Examiner's rejection, as stated, is thus moot.

Applicants note that the precise meaning of the footnote to Table V of Zwick et al. is unclear. For the purpose of this discussion only, assuming the footnote means that ***X*** may be any stem II region of a hammerhead (HH) ribozyme, and the reference to Hertel et al. is merely a reference to clarify the hammerhead nomenclature, then Zwick et al. discloses a hammerhead ribozyme with a generic stem II region which does not anticipate applicants' claimed ribozymes active at low magnesium concentrations. Such an interpretation appears supported by page 23, lines 23-32, of Zwick et al., and by the fact that Hertel et al. is only concerned with nomenclature of hammerhead ribozymes. However, if for the purposes of this discussion only, we assume the footnote means that ***X*** is the stem II region of any one of the two (2) hammerhead ribozymes exemplified in Hertel et al., then neither of the exemplified stem II regions when inserted in place of ***X*** in Zwick et al. results in a sequence that anticipates applicants' claims. Applicants offer these possible interpretations solely for the purposes of alerting the Examiner to the lack of clarity in the footnote. Therefore, applicants respectfully request that the Examiner independently review this footnote and the relevance of Zwick et al. to applicants' claims.

To assist the Examiner in further evaluating the Zwick et al. disclosure, applicants attach with the accompanying Information Disclosure Statement as **Exhibit B** a copy of Hertel et al. 1992 Nucleic Acid Res. 20 3252.

In conclusion, applicants respectfully submit that the objections and rejections set forth in the January 6, 2003 Office Action should be reconsidered and withdrawn in view of the amendments and remarks in this Amendment.

**SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT**

In accordance with their duty of disclosure under 37 C.F.R. §1.56, applicants direct the Examiner's attention to the following reference which is listed on the PTO-1449 form attached hereto as **Exhibit A**. A copy of this reference is attached hereto as **Exhibit B** respectively.

1. Hertel et al. "Numbering system for the hammerhead" 1992 Nucleic Acid Res. 20 3252 **(Exhibit B)**.

This Supplemental Information Disclosure Statement is being submitted after the mailing of the first Office Action but before the mailing date of a final Office Action. Pursuant to 37 C.F.R.§1.97(c), a supplemental information disclosure statement shall be considered by the U.S. Patent Office if filed after the mailing date of the first Office Action but prior to the mailing date of a final Office Action if it is accompanied by the fee set forth in §1.17(p). The fee for filing a supplemental information disclosure statement under 37 C.F. R. §1.97(c), as set forth in §1.17(p) is $180.00 and a check covering this amount is enclosed. Accordingly, applicants request that this Supplemental Information Disclosure Statement be considered.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone at the number provided below.

No fee, other than the enclosed $410.00 fee for a two-month extension of time, and the enclosed $180.00 fee for the Supplemental Information Disclosure Statement, is deemed necessary in connection with the filing of this Amendment. However, if any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:
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6/6/03
Date

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# Numbering system for the hammerhead

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In order to simplify the comparison of data from different laboratories, a uniform numbering system for the 'hammerhead' ribozyme is proposed. The three RNA helices (numbered I, II and II) are specially arranged in Figure 1 as originally proposed (1), but alternate formats (2) are also useful. In Figure 1 we have arbitrarily chosen a hammerhead with a loop 1, a loop 3 and an open helix II ending with dangling nucleotides. Starting with the nucleotide 3′ to the cleavage site, the seventeen nucleotides in the central core are numbered in a clockwise fashion. Six nucleotides in the core (1.1, 2.1, 10.1, 11.1, 15.1 and 16.1) also receive a decimal to indicate that they are the first nucleotide in the helix. Subsequent residues in the three helices are numbered with sequential decimals extending outward from the core. Unless bulges interrupt the helix, this will result in nucleotides with the same decimal pairing with one another (1.3 pairs with 2.3, 10.4 with 11.4, etc.). If the helices form a hairpin, the single stranded loop is named according to the helix number and the residues are giv n decimals starting from the 5′ side of the loop. This system allows a simple definition of the basic features of any hammerhead. The numbering of two specific hammerheads (ASBV and the complex of a designed ribozyme with its target RNA) are given in Figure 2A and 2B.

Following tRNA nomenclature (3), the phosphate 5′ to a nucleotide receives the number of the nucleotide. Thus, cleavage occurs between nucleotides 17 and 1.1 and results in phosphate 1.1 attached to ribose 17 as a 2′,3′ cyclic phosphodiester. Mutations are named by listing the original nucleotide, the positi n number and the mutation. For example, a change of the G residue at position 5 to an A residue would be denoted G5A. A similar method will be used to describe backbone modifications so that a r17d hammerhead contains a 2′deoxy-nucleotide at the cleavage site (and thus will not cleave).

The authors agree to use this nomenclature in future publications and urge the community to do so as well.

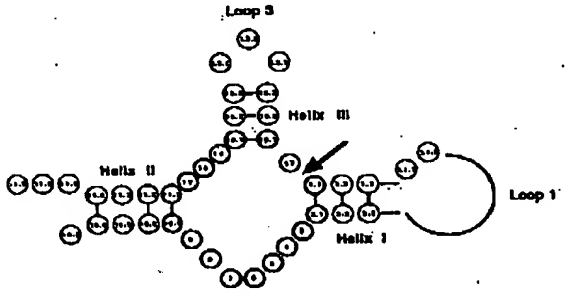


Figure 1.

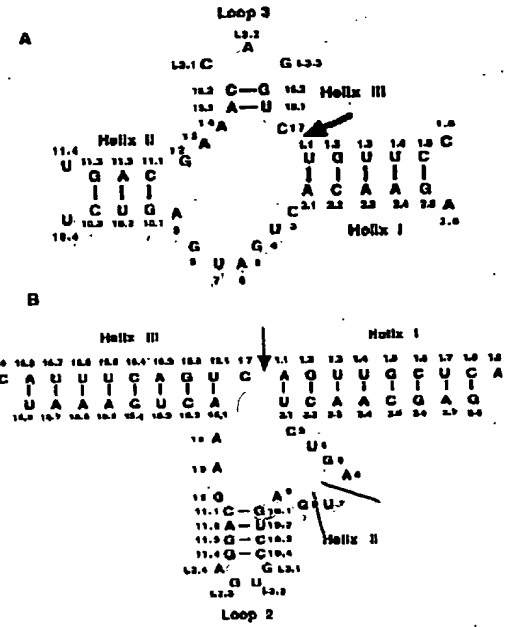


Figure 2.

## REFERENCES

1. Forster,A.C. and Symons,R.H. (1987) *Cell* 49, 211–220.
2. Haseloff,J. and Gedach,W.L. (1988) *Nature* 334, 585–591.
3. Appendix I (1979) In Schimmel,P.R., Söll,D. and Abelson,J.N. (eds.) *Transfer RNA: Structure, Properties, and Recognition*. Cold Spring Harbor Laboratory, New York, pp. 518–519.